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META-ANALYSIS

Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis

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Keywords aged, hospitalisation, medication therapy management, meta-analysis, mortality, polypharmacy

AIM

The aim of the present study was to explore the impact of strategies to reduce polypharmacy on mortality, hospitalization and change in number of drugs.

METHODS

Systematic review and meta-analysis: a systematic literature search targeting patients ≥65 years with polypharmacy (≥4 drugs), focusing on patient-relevant outcome measures, was conducted. We included controlled studies aiming to reduce polypharmacy. Two reviewers independently assessed studies for eligibility, extracted data and evaluated study quality.

RESULTS

Twenty-five studies, including 10 980 participants, were included, comprising 21 randomized controlled trials and four nonrandomized controlled trials. The majority of the included studies aimed at improving quality or the appropriateness of prescribing by eliminating inappropriate and non-evidence-based drugs. These strategies to reduce polypharmacy had no effect on all-cause mortality (odds ratio 1.02; 95% confidence interval 0.84, 1.23). Only single studies found improvements, in terms of reducing the number of hospital admissions, in favour of the intervention group. At baseline, patients were taking, on average, 7.4 drugs in both the intervention and the control groups. At follow-up, the weighted mean number of drugs was reduced (−0.2) in the intervention group but increased (+0.2) in controls.

CONCLUSIONS

There is no convincing evidence that the strategies assessed in the present review are effective in reducing polypharmacy or have an impact on clinically relevant endpoints. Interventions are complex; it is still unclear how best to organize and implement them to achieve a reduction in inappropriate polypharmacy. There is therefore a need to develop more effective strategies to reduce inappropriate polypharmacy and to test them in large, pragmatic randomized controlled trials on effectiveness and feasibility.

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Introduction

Medication in older patients is a complex challenge and needs careful consideration of benefits and potential harms. Complexity arises from age-related changes in body composition and function, together with multiple comorbid conditions, including sensory and cognitive impairment, as well as polypharmacy [1]. The prevalence of polypharmacy in the older population is high in all healthcare settings [2–4]. A large European study [5] showed that 51% of home care patients are taking ≥6 medications per day. In the UK, the average number of medicines prescribed to those aged 65 and over almost doubled from 21.2 to 40.8 items per year within a decade between 1996 and 2006 [6]. Multiple factors contribute to polypharmacy, including chronic diseases [7–9]. As clinical guidelines frequently recommend several drugs for a single disease, guideline adherence inevitably leads to the number of medications exceeding the cut-off point defined as polypharmacy (≥4 or ≥5 drugs) in older persons suffering from several diseases. While the evidence regarding the benefit of polypharmacy is scarce, the evidence regarding the potential harms of polypharmacy is increasing [10]. Polypharmacy substantially increases the risk of adverse drug events (ADEs) [11, 12]. Several studies have confirmed that polypharmacy increases the risk of inappropriate medication use [13–16]. Studies have shown that 80% of ADEs among ambulatory care patients who were hospitalized and up to 90% of ADEs among inpatients were assessed to be preven Table [17–20]. Polypharmacy is also associated with increased hospitalization [10, 21] and mortality [22, 23]. In addition, it involves extensive costs in all healthcare systems [16, 24]. Furthermore, the risk of low adherence to drug therapy is strongly associated with the number of prescribed drugs [25]. There are many reasons to hypothesize that reducing polypharmacy will have a positive impact on health outcome. In recent decades, a variety of strategies and tools have been developed to assess the appropriateness or inappropriateness of medication, which can be explicit (criterion based) or implicit (judgement based) [26]. Both approaches have pros and cons. The disadvantage of explicit measures such as lists of potentially inappropriate medications (PIMs) is that they do not involve the clinical context of an individual patient. Moreover, PIM lists are usually developed by consensus techniques representing expert opinions rather than being based on evidence derived from valid studies. By contrast, implicit measures rely on the judgement of a single clinician or a group of clinicians who use the individual patient's information to assess the appropriateness of medication. However, these approaches are time consuming and costly [27]. Two recently published systematic reviews focused on interventions to reduce the unnecessary use of medications in frail adults with limited life expectancy [28], and on interventions to improve the appropriate use of polypharmacy [29]. The interventions seem beneficial in terms of reducing inappropriate prescribing, although it remained unclear for both author groups whether the respective interventions resulted in clinically significant improvements. The aim of the present systematic review was to explore the impact of strategies to assess and reduce inappropriate polypharmacy in elderly patients on relevant clinical outcome measures such as mortality and hospitalization.

Methods

The review was carried out according to standard protocols for systematic reviews, based on the methodological manuals of the Cochrane collaboration [30] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [31].

Search strategy and selection criteria

A systematic literature search of Ovid Medline (1946 to present) was conducted on 29 March 2013, and of OVID EMBASE (1974 to present), OVID All evidence-based medicine reviews – Cochrane Central Register of Controlled Trials (1991 to present), Cochrane Database of Systematic Reviews (2005 to present), Cochrane Methodology Register (1995 to present), American College of Physicians (ACP) Journal Club (1991 to present), Database of Abstracts of Reviews of Effects (1991 to present), Health Technology Assessment (2001 to present) and National Health Service Economic Evaluation (1995 to present) on 4 June 2013. No filter functions were applied in the literature database searches. All database literature searches were updated on 13 July 2015. The updated search was limited to publication year 2013 to the current date, in order to identify the most recent publications. Search terms are available in Table 1. Population (A), intervention (B, C) and outcome (D) were combined in two separate ways: population (A) AND intervention (B) AND outcome (D) as well as population (A) AND intervention (C) AND outcome (D) (see Table 1 for explanation). The full search strategy is available in Table S1.

Inclusion criteria and methods for the analysis were specified in advance and documented in a protocol (available upon request). A population, intervention, control, outcome and study design (PICOS) framework was developed and used as study selection criteria (Table 2). We included electronic and non-electronic interventions as well as mono- and interdisciplinary approaches aimed at the reduction of inappropriate polypharmacy ('stop interventions'). We considered studies explicitly stating the reduction of polypharmacy as an objective, or implicitly aimed at the optimization of drug appropriateness by discontinuing inappropriate drugs (e.g. tools to detect drug–drug interactions, dosing errors, risk of ADEs, and renal drug dosing). For both study types, the number of drugs had to be reported at baseline and follow-up. Approaches investigating underprescription (e.g. 'start interventions') were excluded because a converse effect on drug quantity was expected. We also excluded interventions focusing on people receiving short-term polypharmacy (e.g. terminally ill or receiving cancer chemotherapy). All types of controlled studies (randomized controlled trials, cluster randomized controlled trials, nonrandomized controlled trials, cohort studies and case control studies) were considered for inclusion. We did not include before-and-after studies, interrupted time-series studies or historically controlled studies as these study designs have a number of serious limitations [30]. Two reviewers independently screened each title and abstract for eligibility by using Reference Manager Professional Edition Version 12 Copyright © 1984–2010 Thomson Reuters. Each article was allocated to either: 'yes', 'no' or 'background' [i.e. systematic reviews, health technology assessments (HTAs)]. Our hand search comprised a review of the bibliographies of all included studies and all systematic

Table 1

Search terms used in OVID Medline

Population (A)	Intervention, electronic strategies (B)	Intervention, non-electronic strategies (C)	Outcome (D)
Aged, geriatrics, frail elderly, veterans, polypharmacy, overprescription, over-prescription, multiple medication, excessive medication, multiple drug, polypharmacotherapy	Hospital information systems, decision support systems, clinical pharmacy information systems, medical order entry systems, drug therapy, computer-assisted, computerized physician order entry, electronic prescribing, adverse drug reaction reporting systems, decision support systems, management, computer assisted drug therapy, drug therapy, computer-assisted, electronic prescription, electronic prescribing, CPOE system, computerised clinical decision support medication errors/pc	Medication appropriateness index, potentially inappropriate medication, the Beers list, PRISCUS list, the STOPP criteria, medication therapy management, drug regimen review, systematic medication review, drug utilization review, medication review, drug counselling, inappropriate prescribing, medication appropriateness	Mortality, morbidity, hospitalization, quality of life, adverse drug event, adverse drug reaction, medication errors, drug therapy/ae, prescription drugs/ae, drug agonism, drug antagonism, drug inverse agonism, drug interactions, ADR, ADE, utilization of resources, number of medications, hospital admission, drug related admissions, drug-related readmissions, drug-related problems, drug errors, safety-based drug withdrawals, hospitality

All search terms were entered as MeSH terms and text words. CPOE, computerized physician order entry; STOPP, Screening Tool of Older Persons' Potentially Inappropriate Prescriptions; PRISCUS, list of potentially inappropriate medication for older people developed by the German PRISCUS-research network

Table 2

PICOS framework: study eligibility criteria

Population	• Patients with polypharmacy: four or more prescribed or nonprescribed drugs or 80% of study population taking ≥4 drugs • The number of drugs must be reported at baseline and follow-up • Older patients: age ≥ 65 years or 80% of study population aged ≥65 years • All healthcare settings (i.e. hospital, primary care, nursing home)	
Interventions	Electronic strategies to reduce polypharmacy: • CPOE • CDS systems • Others	Non-electronic strategies to reduce polypharmacy: • Potentially inappropriate medication: – The updated Beers list – The PRISCUS list – Other PIM lists (e.g. Beers list older versions) • Garfinkel algorithm • Medication Appropriateness Index • The STOPP criteria • Other tools identified • Pharmacist-led interventions
Control	No intervention or usual care (other comparable intervention)	
Outcome	**Primary outcomes:** • Mortality • Hospitalization • Change in number of drugs	**Secondary outcomes (results available in supplements):** • New morbidity • Change in quality of life • Changes of physical and mental functioning • Adverse drug event • Adverse drug reaction • Medication error • Inappropriate medication • Adverse event after discontinuation of medication (safety) • Process of care (feasibility) • User/patient satisfaction/acceptance • Adherence to medication • Resource utilization (e.g. use of healthcare resources) • Costs (e.g. reduction of drug costs, hospital costs)/cost-effectiveness
Study design	RCTs, cluster RCTs, nonrandomized controlled clinical trials, cohort and case control studies	

CDS, clinical decision support; CPOE, computerized physician order entry; PIM, potentially inappropriate medications; PICOS, population, intervention, control, outcome and study design; PRISCUS list, a list of potentially inappropriate medication for older people developed by the German PRISCUS research network; RCT, randomized controlled trial; STOPP, Screening Tool of Older Persons' potentially inappropriate Prescriptions.

reviews identified as 'background' literature. We also screened HTA institutions to find relevant grey literature (e.g. the National Institute for Health and Clinical Excellence, the Canadian Agency for Drugs and Technologies in Health, the Swedish Agency for Health Technology Assessment and Assessment of Social Services). We then obtained full-text copies of all publications considered to be of potential relevance. Disagreement between the two researchers was resolved by discussion, and if necessary by arbitration by the senior researcher (AS).

Data extraction and synthesis

We developed a data extraction sheet based on the Cochrane Consumers and Communication Review Group's data extraction template [46], pilot-tested it on four randomly selected included studies and refined it accordingly. One author (TJ, MA, JH, AK) extracted the data and a second author (CL, CS, EM, SK) independently extracted the data and then checked the completeness by reviewing the extraction tables of the first author and checking the extracted data in the full-text articles. Disagreements were resolved by discussion between the two authors; if no agreement could be reached, a third author was consulted (AS). If essential information was lacking in a paper, we contacted corresponding authors and asked them to provide supplements. The quality of the evidence was assessed by three authors (TJ, MA, SK) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. The quality of the body of evidence for each primary outcome was evaluated according to the five GRADE considerations: study limitations; consistency of effect; imprecision; indirectness; publication bias [32]. Risk of bias was assessed according to the Cochrane Collaboration Handbook [30] by the authors involved in the data extraction (see above).

The methodology of our meta-analysis varied depending on the quality, design and heterogeneity of included studies. Statistical heterogeneity was calculated using the I^2 statistics. However, the research studies showed high levels of clinical heterogeneity (see below), making true homogeneity of effect highly unlikely and we therefore applied random-effects meta-analysis, regardless of the I^2 value [33]. We analysed mortality as a binary outcome using a DerSimonian–Laird random-effects model, with effects reported as odds ratios (ORs). We performed a sensitivity analysis for pooled results based on methodological quality and length of follow-up (pooling studies of the same design (e.g. randomized controlled trials and cluster randomized controlled trials) to assess the overall effect.

Results

Study selection

We identified 25 258 potentially relevant records. After removal of 6206 duplicates, 19 052 titles and abstracts were screened for eligibility. Of these, 394 articles appeared to meet the inclusion criteria. Assessment of full texts revealed that 372 of the 394 studies had to be excluded. A detailed list of excluded studies, with reasons, is available in Table S2. Three additional studies were included via hand search [34–36]. Finally, 25 studies [34–58] were included in the systematic review (Figure 1).

Study characteristics

The 25 included studies comprised 17 randomized controlled trials [34–36, 38–42, 44–47, 50, 51, 54, 57, 58], four cluster randomized controlled trials [37, 43, 48, 53] and four nonrandomised controlled trials [49, 52, 55, 56]. Length of follow-up ranged from 6 weeks [45] to 18 months [34, 44]. A total of 10 980 participants were included in the systematic review (range 79–2454 per study). The mean age of study participants ranged from 69.7 to 87.7 years and the percentage of male participants ranged from 20% to 100%. Detailed characteristics of the included 25 studies are provided in Table S3.

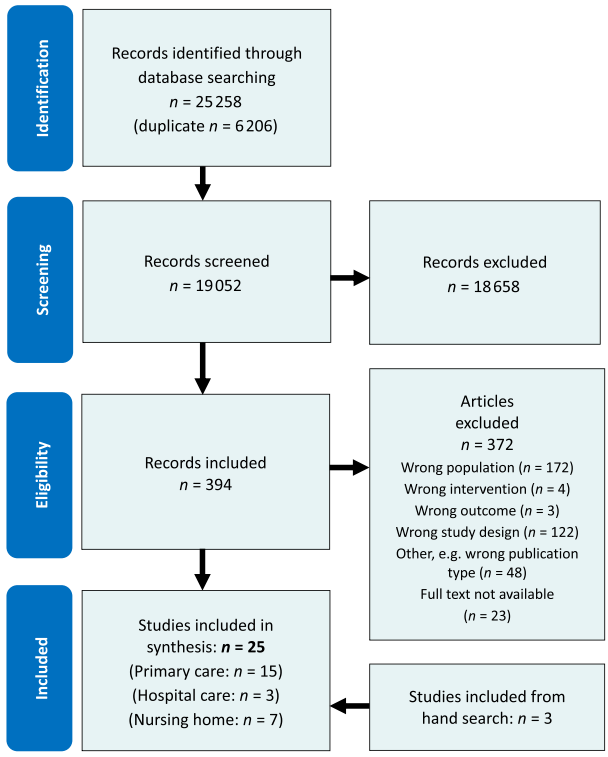

Figure 1
Study selection process [Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram]

Study objectives and settings

The majority of the studies considered strategies aimed at improving the quality (appropriateness) of the medication regimen by removing inappropriate prescriptions, without explicitly stating the reduction in the number of drugs as an objective of the study [35–37, 39, 41, 42, 45, 46, 48, 50–55, 57, 58]. Only five studies aimed explicitly to reduce the quantity of drugs [38, 40, 43, 47, 56] or the number of potential drug-related problems [49] or actual drug-related problems, such as noncompliance, expired indication, duplication, inappropriate dosage, off-label use, contraindications, etc. [34, 44]. The objectives of all included studies are presented in Table 3.

The identified approaches included the following care settings: general practitioner surgeries [34, 41–51, 58], primary care centres/general practitioner outpatient clinic [38, 40], including home-dwelling and/or community-dwelling subjects. Moreover, we identified strategies carried out in an internal medical clinic [56], in a hospital [35], in a chronic care geriatric facility [39], in residential hospitals with continuous care wards [57], in nursing homes [36, 52–55] and in an assisted living facility [37].

Table 3

Summary of objectives

Author	Objective
Pharmacist-led interventions (13)	
Primary care (9)	
Bernsten *et al.* [34]	The aim of the study was to measure the outcomes of a structured pharmaceutical care programme provided to elderly patients by community pharmacists in a multicentre international study performed in seven European countries
Bregnhøj *et al.* [48]	The aim of the study was to evaluate the effect of a combined or single educational intervention on the prescribing behaviour of general practitioners (regarding overall appropriateness)
Hanlon *et al.* [41]	The aim of the study was to evaluate the effect of clinical pharmacist interventions involving elderly outpatients with polypharmacy and their primary care physicians.
Lenaghan *et al.* [46]	The aim of the study was to assess whether home-based medication review by a pharmacist for older patients at-risk in a primary care setting can reduce hospital admissions
Lenander *et al.* [38]	The aim of the study was to determine whether a pharmacist-led medication review in primary care reduces the number of drugs and the number of drug-related problems
Milos *et al.* [51]	The aim of the study was to assess the impact of pharmacist-led medication reviews on the number of patients using potentially inappropriate medications and the number of patients using ≥10 drugs and ≥3 psychotropic drugs, and to describe the types of drug-related problems identified
Sellors *e t al.* [43]	The aim of the study was to examine whether an intervention by a specially trained pharmacist could reduce the number of daily medication units taken by elderly patients, as well as costs and healthcare use
Sturgess *et al.* [44]	The aim of the study was to measure the outcomes of a structured pharmaceutical care programme provided to elderly patients by community pharmacists
Vinks *et al.* [49]	The aim of the study was to investigate whether a community pharmacist-led intervention reduces the number of potential drug-related problems
Nursing home (2)	
Frankenthal *et al.* [39]	The aim of the study was to evaluate the effect of screening medications according to STOPP/START criteria on the number of hospitalizations and falls, functioning, quality of life and medication costs of residents in a geriatric facility
Zermansky *et al.* [54]	The aim of the study was to measure the impact of a pharmacist-conducted clinical medication review with elderly care home residents
Hospital (2)	
Kroenke and Pinholt [56]	The aim of the study was to determine the effectiveness of specific feedback to prescribing physicians regarding the reduction of polypharmacy in elderly outpatients
Naunton and Peterson [35]	The aim of the study was to evaluate pharmacist-conducted follow-up at home of high-risk elderly patients discharged from hospital
Author	**Objective**
Physician-led interventions (4)	
Primary care (3)	
Olsson *et al.* [50]	The aim of the study was to examine whether prescription reviews sent from a primary care physician to other primary care physicians could affect prescription quality and the patient's quality of life, and also whether there were any additive effects by encouraging the patients to question their drug treatment by giving them their medication record
Ortega Blanco [40]	The aim of the study was to evaluate the effectiveness of a structured intervention through the Dader method on patients with polypharmacy of a sanitary district to reduce the number of drugs prescribed
Weber *et al.* [47]	The aim of the study was to evaluate an electronic medical record-based intervention to reduce overall medication use, psychoactive medication use and the occurrence of falls in an ambulatory elderly population at risk for falls
Nursing home (1)	
Olsson [55]	The aim of the study was to evaluate whether patient-focused drug surveillance was associated with a higher quality of drug treatment at nursing homes

(continues)

Table 3
(Continued)

Author	Objective
Multidisciplinary team-led interventions (8)	
Primary care (3)	
Allard [42]	The aim of the study was to evaluate the impact of an intervention program targeting physicians with the aim of reducing the number of potentially inappropriate prescriptions given to elderly patients
Lampela *et al.* [58]	The aim of the study was to investigate the performance of a comprehensive geriatric assessment with regard to medication changes and to determine the persistence of these changes over a 1-year period
Williams *et al.* [45]	The aim of the study was to determine whether a medication review by a specialized team would promote regimen changes or simplify medication regimen in elder persons taking multiple medications and to measure the effect of regimen changes on monthly cost and functioning
Nursing home (4)	
Claesson and Schmidt. [36]	The aim of the study was to describe the overall drug use in Swedish nursing homes and to comment on the impact of regular multidisciplinary team interventions on the quantity of inappropriate medications
Crotty [53]	The aim of the study was to evaluate the impact of multidisciplinary case conferences on the appropriateness of medications and on patient behaviour in high-level residential aged care facilities
King and Roberts [52]	The aim of the study was to determine whether multidisciplinary case conference reviews improved outcomes for nursing home residents, and the effects of this team approach to resident care on carers, including the hands-on carers employed by the nursing home, and health professionals
Pitkälä *et al.* [37]	The aim of the study was to investigate the effect of nurse training on the use of potentially harmful medications and to explore the effect of nurse training on residents' quality of life, health service utilization, and mortality
Hospital (1)	
Pope *et al.* [57]	The aim of the study was to evaluate specialist geriatric input and medication review in patients in high-dependency continuing care

START, Screening Tool to Alert Doctors to Right (i.e. indicated, appropriate) Treatment; STOPP, Screening Tool of Older Persons' potentially inappropriate Prescriptions.

Description of interventions

We identified three main categories of interventions: pharmacist-led interventions, physician-led interventions or multidisciplinary team-led interventions. The identified strategies were highly complex. They varied in terms of assessment of participants' drug regimens, performance of medication reviews, forwarding recommendations to the responsible physician and the involvement of patients.

Pharmacist-led interventions

Thirteen studies were categorized as pharmacist-led interventions, of which nine were conducted in primary care [34, 38, 41, 43, 44, 46, 48, 49, 51], two studies in nursing homes [39, 54] and another two in hospitals [40, 56]. Two studies [41, 48] assessed the appropriateness of medication by using the Medication Appropriateness Index (MAI); Milos *et al.* [51] used the national guidelines (PIM list) of the Swedish National Board of Health and Welfare [59], and Frankenthal *et al.* [39] used the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP)/Screening Tool to Alert Doctors to Right (i.e. indicated, appropriate) Treatment (START) criteria. In all other studies, the appropriateness of medication use was assessed by experts, or the authors did not provide sufficient information about the medication review process. In six studies, the responsible physicians received written recommendations and were contacted personally by the pharmacist performing the medication review [35, 41, 43, 48, 51, 56]. In three studies, the pharmacist contacted the responsible physicians personally [39, 46, 49]. In four studies, it was unclear how recommendations were forwarded to the responsible physicians [34, 38, 44, 54]. Patient education was part of the intervention in six studies [34, 35, 38, 41, 44, 46], and three studies [34, 44, 46] implemented compliance-improving strategies. Medication changes were discussed with patients in three studies [46, 49, 54], and five studies did not provide sufficient information about patients' involvement.

Physician-led interventions

In three studies, a physician led the intervention and performed the medication review [40, 50, 55]. A single study was led either by a physician or a pharmacist, both performing medication reviews independently [47]. Three studies were carried out in primary care settings [40, 47, 50], and one in nursing homes [55]. No checklists, such as MAI or Beers list, were used. Written recommendations were sent to the physician responsible for patient care [50] via the electronic medical record [47]. In Olsson *et al.* [55], the physicians responsible for patient care were educated to perform the medication reviews themselves. In another study by Olsson *et al.* [50], patients in the second intervention group received written information about their drug regimen and indications to enable participation in their drug treatment.

Multidisciplinary team-led interventions

Eight multidisciplinary team-led interventions were identified [36, 37, 42, 45, 52, 53, 57, 58]. They were carried out in primary care settings [42, 45, 58], nursing homes [36, 37, 52, 53] or inpatient care [57]. Two studies [45, 53] assessed appropriate medication use with the MAI and two further studies [57, 58] used the Beers list. Allard [42] used a list to identify potentially inappropriate prescriptions developed by the Quebec Committee on Drug Use in the Elderly [60]. The medication review process, assessed by experts, was unclear in two trials [45, 58]. The developed recommendations were sent to each patient's physician, supplemented by relevant scientific literature [42, 57], or the responsible physician attended the multidisciplinary meetings [36, 52, 53]. In three studies, it remained unclear how the recommendations of the medication review were communicated to the responsible physicians [37, 45, 58]. In the study by Williams *et al*. [45], potential medication changes were discussed with each patient to achieve full acceptance. Allard [42] stated that patients were not informed about the result of the medication review, and in six trials study authors did not provide sufficient information about patients' involvement [36, 37, 52, 53, 57, 58].

Reporting of outcomes

The included studies were highly heterogeneous in terms of study quality, study designs, interventions, settings, participants, reporting and definitions of outcome measurements, as well as length of follow-up. The controls received usual care based on the setting in which the study was carried out. Therefore, it was only justifiable to pool the results of studies providing information on all-cause mortality during the study period and perform a meta-analysis of these studies regarding mortality. All other outcome measures of interest are reported as a narrative summary.

Risk of bias in the included studies

A summary of risk of bias is presented in Table S4. The main limitations contributing to risk of bias were related to the design (e.g. inadequate randomization, intent-to-treat analysis, sample size and power calculation) or execution of the studies.

Effects of interventions – primary outcome results

Mortality. Nineteen studies reported on all-cause mortality during the study period [35, 37, 39, 41–44, 46–55, 57, 58]. Length of study period ranged from 2 months to 18 months. The mortality rates in the study by King [52] were adjusted for the period of time that the resident was living in the nursing home and were therefore not considered in the meta-analysis. Seven studies [35, 37, 46, 52, 54, 55, 57] defined mortality as an outcome measure; all others registered death as lost to follow-up. We pooled data from 18 studies [35, 37, 39, 41–44, 46–51, 53–55, 57, 58], including 3110 (intervention) and 2893 (control) participants. The strategies to reduce polypharmacy assessed in these studies had no effect on all-cause mortality [OR 1.02 (95% CI 0.84, 1.23)]. Statistical heterogeneity was low (I^2 = 8%; P = 0.362) (Figure 2), implying a consistent lack of effect across the studies. Our sensitivity analysis detected no effect on all-cause mortality when pooling randomized controlled trials (Figure 3). We performed a subgroup meta-

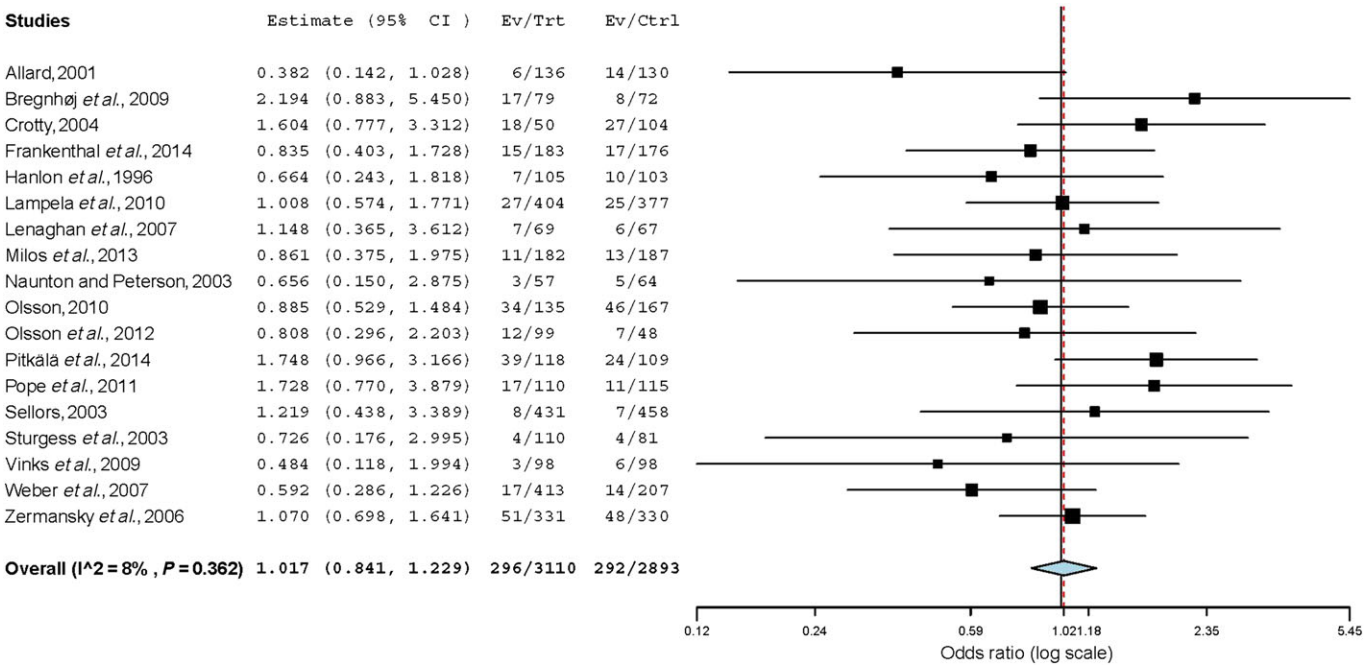

Figure 2

Data and analysis on all-cause mortality during the study period, using binary random effects and the DerSimonian-Laird method. CI, confidence interval; Ctrl, control; Ev, event; Trt, treatment/intervention

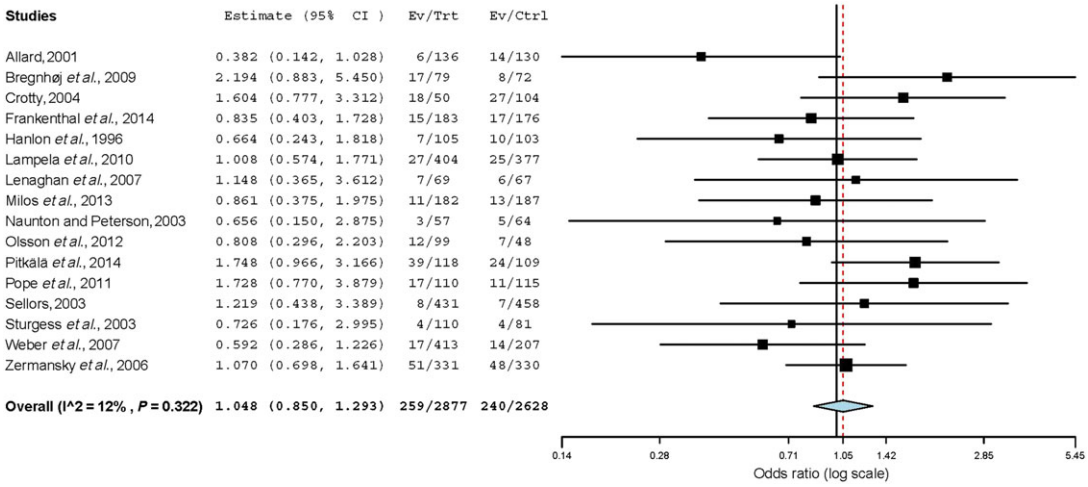

Figure 3

Data and analysis on all-cause mortality during the study period (only randomized controlled trials and cluster randomized controlled trials), binary random effects and the DerSimonian-Laird method. CI, confidence interval; Ctrl, control; Ev, event; Trt, treatment/intervention

analysis to explore if the effect size (OR) was related to length of follow-up. One subgroup analysis included studies with short follow-up periods (2–6 months) [35, 43, 46, 49, 51, 53, 54, 57], and another included studies with long follow-up periods (12–18 months) [37, 39, 41, 42, 44, 47, 48, 50, 55, 58]. No significant differences were found in either of the subgroup analyses. However, regarding ORs, there seems to be a trend towards reduced mortality if follow-up periods are longer [long follow-up: OR 0.93 (95% CI 0.69, 1.24); short follow-up: OR 1.13 (95% CI 0.86, 1.50)]. Low level of inconsistency was detected in the subgroup analyses (Figures 4, 5). No single study exploring the effect on all-cause mortality as an outcome measure showed any significant effect in favour of the intervention group [35, 37, 46, 52, 54, 55, 57]. The included studies were heterogeneous, as described above. However, we decided to pool data on all-cause mortality owing to the fact that mortality was a 'hard' primary endpoint. The studies were not similar enough to combine for other endpoints. Outcome measures were measured differently over different follow-up periods, so it was not possible to pool them. An overview of all included studies and a description for each outcome, including the way the outcome was treated [e.g. OR, relative risk (RR), etc.], and follow-up times are available in Table S3.

Hospitalization. Eleven of 25 studies reported on hospitalization as an outcome measure [34, 35, 37–39, 43, 44, 46, 54, 55, 57]. Only two studies found a significant effect of the intervention on hospitalization. In Naunton *et al.* [35, 37], 45% of the participants in the control group were readmitted (unplanned) during the 90-day follow-up, compared with 28% in the intervention group (chi-square, $P = 0.05$), but there was no significant difference between groups in the total number of days in the hospital ($P = 0.06$). In Pitkälä *et al.* [37], participants in the intervention group had significantly fewer hospital days (1.4/person/year; 95% CI 1.2, 1.6) compared with participants in the control group (2.3/person/year; 95% CI 2.1, 2.7) (incidence rate ratio 0.60; 95% CI 0.49, 0.75, $P < 0.001$, adjusted for age, gender and comorbidities). Five studies assessed all-cause hospital admissions per patient as an outcome measure. No significant differences between groups were seen in all-cause hospital admissions [38, 39, 43, 54, 55]. In Lenaghan *et al.* [46], the

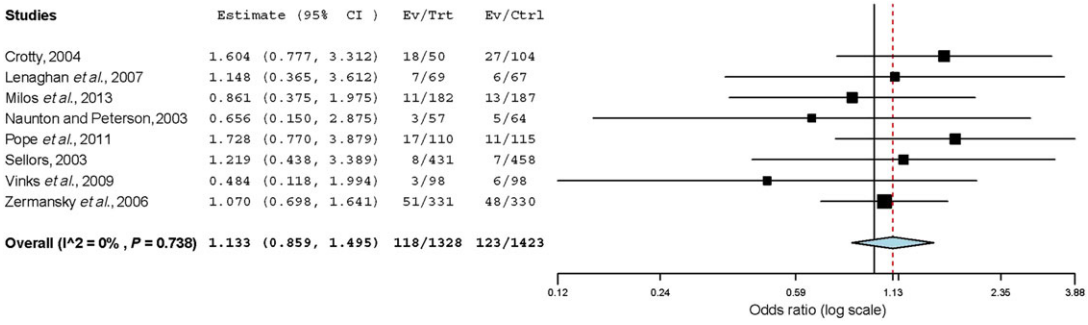

Figure 4

Subgroup analysis on all-cause mortality during the study period including only studies with short follow-ups (2–6 months), binary random effects and the DerSimonian-Laird method. CI, confidence interval; Ctrl, control; Ev, event; Trt, treatment/intervention

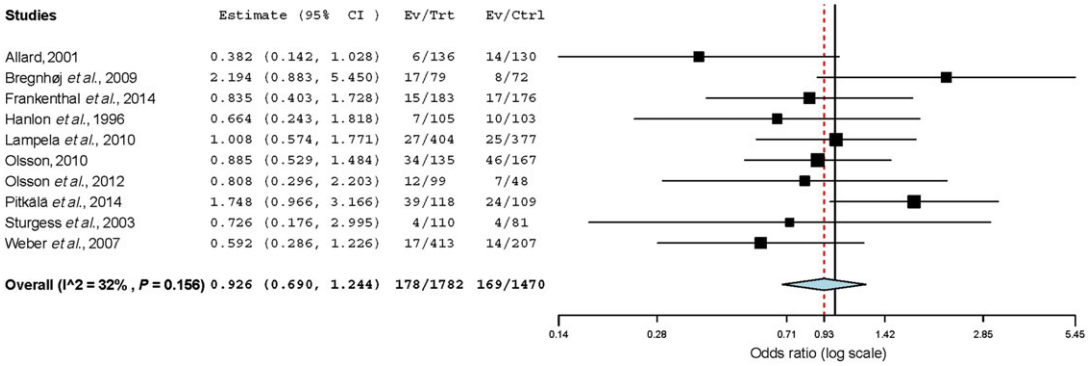

Figure 5

Subgroup analysis on all-cause mortality during study period including only studies with long follow-ups (12–18 months), binary random effects and the DerSimonian-Laird method. CI, confidence interval; Ctrl, control; Ev, event; Trt, treatment/intervention

number of non-elective hospital admissions was reduced by 8% in favour of the intervention group but the difference was not significant (RR 0.92; 95% CI 0.50, 1.70, $P = 0.80$). In Pope *et al.* [57], no difference between groups regarding acute hospital admissions were detected ($P = 0.21$). In addition, the two studies reporting on hospital admissions within a European multicentre study found no significant difference between intervention and control groups [34, 44]. Sellors *et al.* [43] could not show any significant difference in drug-related hospital stays between the intervention and control groups (RR 1.01; 95% CI 0.51, 2.02). In Lenander *et al.* [38], the length of hospitalization during the 12-month follow-up period was lower in the intervention group compared with the control group but the difference was not significant (mean 12 days *vs.* 18 days).

Changes in number of drugs. Different definitions of number of drugs were used. Twenty-three studies provided data on either the number of prescribed drugs only [34, 36, 39, 41, 42, 44–49, 52, 53, 57] or the number of prescribed drugs taken on a regular basis [35, 37, 40, 50, 51, 54–56, 58]. Two studies [38, 43] included prescribed and over-the-counter drugs. Most studies analysed the mean number of drugs but two [35, 50] reported the median number. We calculated mean changes in the number of drugs as the mean difference in the intervention group minus the mean difference in controls. An overview regarding the number of drugs is provided in Table 4. The weighted mean, including prescribed drugs and prescribed drugs taken on a regular basis, at baseline was 7.4 drugs per patient in both groups. The length of follow-up ranged from 1.5 months to 18 months. At follow-up, the weighted mean number of drugs was reduced (−0.2) in the intervention group but increased (+0.2) in controls. It was not possible to calculate the statistical significance of this difference because most studies did not report standard deviation. Only three trials found significant differences by performing a between-groups analysis based on mean differences (baseline to follow-up) [38, 45, 46]. In Williams *et al.* [45], the number of prescribed drugs after the 6-week visit was reduced in the intervention group compared with controls by 0.98 drugs (95% CI 1.35, 609; $P = 0.001$) [*sic*]. In Lenaghan *et al.* [46], the mean difference in prescribed drugs over 6 months was −0.87 drugs (95% CI −1.66, −0.08; $P = 0.03$) in favour of the intervention group. In Lenander *et al.* [38], the number of prescribed and nonprescribed drugs was reduced by 0.7 drugs per patient, but in the control group there was no change. The change in the number of drugs thus differed significantly between intervention and control groups ($P < 0.046$).

Effects of interventions – secondary outcome results

The results of the secondary endpoints defined in the methods section are provided in Table S5. Overall, the effects of interventions on our predefined secondary outcomes were minimal.

Quality assessment – the GRADE approach

We used the GRADE Pro assessment tool to evaluate the quality of studies reporting on mortality and hospitalization (Figure 6). Risk of bias should be reported by outcome ('critical endpoints') as risk of bias may vary across outcomes (e.g. loss to follow-up may be far lower for all-cause mortality than for quality of life) [61]. A summary of the risk of bias across studies assessed for the outcome measures mortality and hospitalization is presented in Tables S6 and S7.

Mortality. In total, 19 studies provide data on mortality. Only 18 of these studies explored all-cause mortality during the study period [35, 37, 39, 41–44, 46–51, 53–55, 57, 58]. We found serious limitations in design and implementation in several studies providing data on mortality. The quality of evidence was downgraded by imprecise results, small numbers of events and wide confidence intervals.

Hospitalization. Eleven studies [34, 35, 37–39, 43, 44, 46, 54, 55, 57] provided information on the hospitalization of participants during the study period. We found serious limitations in design and implementation in multiple studies reporting on hospitalization. The quality of evidence was downgraded by imprecise results, small numbers of events and wide confidence intervals.

Level of evidence. The quality of the evidence on strategies to reduce polypharmacy was rated as low to very low, and any estimate of effect is very uncertain. In summary, there

Table 4

Number of drugs at baseline and follow-up

Author	Length of follow-up (months)	Intervention group (A)				Control group (B)				*P*-value, follow-up analysis between groups	Mean difference between groups (A–B)†
		n	Mean number of drugs*		Diff. (A)	*n*	Mean number of drugs*		Diff. (B)		
			Baseline	Follow-up			Baseline	Follow-up			
Allard [42]‡	12	127	6.1	5.8	−0.3	116	6.5	6.4	−0.1	0.46	−0.2
Bernsten *et al.* [34]‡	18	1290	7.1	7.1	0.0	1164	6.9	7.0	0.1	>0.05	−0.1
Bregnhøj *et al.* [48]‡	Not reported (at least 6)	49	7.9	7.0	−0.9	64	7.5	7.7	0.2	Not reported	−1.1
Claesson and Schmidt [36]‡	14	626	7.5	7.8	0.3	1228	7.8	8.2	0.4	Not reported	−0.1
Crotty [53]‡	3	50	6.0	5.5	−0.5	54	5.9	5.7	−0.2	Not reported	−0.3
Frankenthal *et al.* [39]‡	12	BL: 183	8.8	7.3	−1.5	BL: 176	8.2	8.9	0,7	<0.001	2.2
		FU: 160				FU: 146					
Hanlon *et al.* [41]‡	12	105	7.6	6.9	−0.7	103	8.2	7.9	−0.3	0.83	−0.4
King and Roberts [52]‡	10	75	8.3	8.0	−0.3	170	7.5	7.5	0.0	Not reported	−0.3
Kroenke and Pinholt [56]§	6	38	5.9	5.4	−0.5	41	5.8	5.8	0.0	Not reported	−0.5
Lampela *et al.* [58]§	12	331	4.7	5.2	0.5	313	4.8	5.2	0.4	Not reported	0.1
Lenaghan *et al.* [46]‡	6	56	9.0	8.7	−0.3	49	9.6	10.3	0.7	Not reported	−0.90 (95% CI − 1.66, −0.08, $P = 0.03$)
Lenander *et al.* [38]**	12	75	8.6	7.9	−0,7	66	7.4	7.4	0.0	Not reported	−0.7 ($P < 0.046$)
Milos *et al.* [51]§	2	182	9.3	8.8	−0.5	187	9.7	9.6	−0.1	Not reported	−0.4
Naunton and Peterson [35] §,††	3	57	8.0	8.0	0.0	64	8.0	8.0	0.0	Not reported	Not reported††
Olsson [55]§	12	135	6.9	6.5	−0.4	167	7.5	7.8	0.3	<0.01	−0.8
Olsson *et al.* [50]‡, ¶,††	12	48	8.0	9.0	1.0	50	10.0	10.0	0.0	Not reported	Not reported††
		49	10.0	11.0	1.0					Not reported	Not reported††
Ortega Blanco [40]§	not reported (max. 12)	56	8.6	7.5	−1.1	57	9.1	10.8	1.7	<0.0001	2.8
Pitkälä *et al.* [37]§	12	118	7.5	8.6	1.1	109	7.8	7.6	−0.2	Not reported	1.3
Pope *et al.* [57]‡	6	110	11.6	11.1	−0.6	115	11.1	11.5	0.4	Not reported	−1.0
Sellors [43]**	5	431	8.0	8.0	0.0	458	8.1	7.9	−0.2	0.87	0.2
Sturgess *et al.* [44]‡	18	110	5.9	6.2	0.3	81	6.7	6.7	0.0	>0.05	0.3

(continues)

Table 4
(Continued)

Author	Length of follow-up (months)	Intervention group (A)				Control group (B)				*P*-value, follow-up analysis between groups	Mean difference between groups (A–B)†
		n	Mean number of drugs*		Diff. (A)	*n*	Mean number of drugs*		Diff. (B)		
			Baseline	Follow-up			Baseline	Follow-up			
Vinks *et al.* [49]‡	4	87	8.8	8.3	−0.5	87	8.5	8.4	−0.1	Not reported	−0.4
Weber *et al.* [47]‡	15	413	7.7	7.9	0.2	207	7.5	7.6	0.1	n.s.	0.1
Williams *et al.* [45]‡	1.5	57	6.6	5.6	−1.0	76	7.7	7.7	0.0	Not reported	−0.98 ($P = 0.001$)
Zermansky *et al.* [54]§	6	331	6.9	6.7	−0.2	330	6.9	6.9	0.0	Not reported	−0.2

A, intervention group; B, control group; BL, baseline; CI, confidence interval; Diff., difference; FU, follow-up; max., maximum; n.s., not significant (*P*-value is not reported). *Standard deviation could not be calculated because it was not reported in all studies. †Self-calculated values; differences were calculated as difference intervention (A) minus difference controls (B). ‡Prescribed drugs. §Prescribed drugs taken on a regular basis. ¶Study included two intervention groups. **Prescribed and over-the-counter drugs. ††Authors report on median number of drugs.

was insufficient evidence on the effect of strategies to reduce polypharmacy on patient relevant outcomes such as mortality and hospitalization.

Discussion

Summary of main results

In total, 25 studies (17 randomized controlled trials, four cluster randomized controlled trials and four nonrandomized controlled intervention studies) on strategies to reduce polypharmacy were included in the present systematic review. The majority of studies aimed to improve the quality of the medication regime by eliminating inappropriate prescriptions. Only five studies explicitly aimed to reduce the quantity of medication use. Our meta-analysis on all-cause mortality during the study period showed no effect in favour of the intervention group. In a single study, fewer participants in the intervention group were readmitted to the hospital (unplanned) during the 90-day follow-up, compared with controls [35]. In another study [37], the length of hospital stay was shorter in the intervention group compared with controls, although significant differences between groups existed at baseline, compromising the result. In all other studies, no significant differences between groups were seen in hospital admissions [34, 38, 39, 43, 44, 46, 54, 55, 57]. With the exception of three studies, there was no substantial change regarding the number of drugs taken. Thus, the overall evidence regarding the effectiveness of any of the evaluated interventions to improve outcome by reducing polypharmacy and inappropriate prescribing is very limited.

Health professionals from various fields were involved in the medication reviews and development of recommendations, and they would therefore have had different approaches and attitudes. As a consequence, the studies used a variety of methods for the medication review. Participants' (appropriate) medication use was reviewed using different methods (tools and instruments), from which we identified four main methods: checklists (e.g. MAI), drug–drug interactions tools (e.g. software, lists), reconciliation methods and expert opinion, based either on a single pharmacist or physician, or a multidisciplinary team (case conferences with consensus-based discussion on medication quality). All studies using consensus or expert opinion lack reproducibility owing to a lack of information on the process of drug evaluation. Future intervention studies thus should provide sufficient information regarding study design, data acquisition and use of decision support tools. Given the demographic development of the population and the growing burden of multimorbidity and polytherapy, research efforts should be made available in a transparent and reproducible way. The methodology of the medication review is one key issue in interventions aimed at improving the quality of medication use (and/or to reduce inappropriate medication use). A wide range of methods was identified but it remained unclear which was the most suitable.

Strengths and limitations

The present systematic review was based on a comprehensive database literature search. Studies were selected according to

Outcomes	No of Participants (studies) Study period	Quality of the evidence (GRADE)	Effect (95 % CI)	Anticipated absolute effects	
				Risk with usual care or other comparable intervention	Risk difference with strategies to reduce polypharmacy (95 % CI)
Mortality All-cause mortality during study period	6003 (18 studies*) 2–18 months	⊕⊕⊖⊖ **LOW**† due to risk of bias, imprecision	**OR 1.017** (0.84 to 1.23)	**100 per 1000**	**5 fewer per 1000** (from 22 more to 16 less)
Hospitalization Drug-related hospitals stays	788 (1 study‡) 5 months	⊕⊖⊖⊖ **VERY LOW**§ due to risk of bias, imprecision	not applicable¶		-
Hospitalization All admissions to hospital	2198 (5 studies**) 5–12 months	⊕⊖⊖⊖ **VERY LOW**†† due to risk of bias, imprecision	not applicable¶		-
Hospitalization Total numbers of non-elective hospital admissions	359 (2 studies‡‡) 6 months	⊕⊖⊖⊖ **VERY LOW**§§ due to risk of bias, imprecision	not applicable¶		-
Hospitalization Hospitalizations, % (one or more hospitalisations)	0 (2 studies¶¶) 18 months	⊕⊖⊖⊖ **VERY LOW***** due to risk of bias, imprecision	not applicable¶		-
Hospitalization Unplanned readmissions	121 (1 study†††) 3 months	⊕⊖⊖⊖ **VERY LOW**‡‡‡ due to risk of bias, imprecision	not estimable (single study)		-
Hospitalization Length of hospital stay, in days	489 (3 studies§§§) 3–12 months	⊕⊖⊖⊖ **VERY LOW**¶¶¶ due to risk of bias, imprecision	not estimable****		-

Figure 6

Quality assessments: the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. CI, confidence interval; cRCT, cluster RCT; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk. CI confidence interval; RR Risk ratio; OR Odds ratio. *Twelve RCTs, four cRCT, and two non-randomized controlled intervention studies. †The quality of evidence is downgraded by imprecise results, small number of events and wide confidence interval. An appropriate random sequence generation was used in eight. Allocation concealment was adequate in six studies. Seven studies defined mortality as an outcome measure, all other studies reported on mortality as lost to follow-up. ‡One cRCT. §The quality of evidence is downgraded by imprecise results, small number of events and wide confidence interval. Allocation concealment was unclear. Lack of blinding of participants, professionals and outcome assessors. A per protocol analysis was performed. ¶Clinical and methodology heterogeneity exist – too dissimilar; does not make sense to pool statistically. **Three RCTs, one cRCT, and one non-randomized controlled intervention study. ††The quality of evidence is downgraded by imprecise results, small number of events and wide confidence interval. Randomisation process unclear. Lack of blinding of participants, professionals and outcome assessors. Only one study used an intent-to-treat analysis. ‡‡Two RCTs. §§The quality of evidence is downgraded by imprecise results, small number of events and wide confidence interval. Unclear allocation concealment. High risk of contamination bias. An intent-to-treat analysis was performed in one study. ¶¶One multicentre RCT (data from Sturgess *et al.* 2003 is included in this trial). ***The quality of evidence is downgraded by study limitations. Unclear how randomisation was performed. Outcome assessors were not blinded. A per-protocol analysis was performed. Lack of information regarding patient selection. †††One RCT. ‡‡‡The quality of evidence is downgraded by imprecise results, small number of events and wide confidence interval. A per protocol analysis was performed. No power calculation. Allocation concealment and blinding of outcome assessment unclear. §§§Two RCTs and one cRCT. ¶¶¶The quality of evidence is downgraded by imprecise results, small number of events and wide confidence interval. Allocation concealment was unclear. Lack of blinding of participants, professionals and outcome assessors. A per protocol analysis was performed in two studies. Important baseline differences in one study. ****Studies do not provide information on means with standard deviations. Not possible to pool data

a predefined PICOS framework (unpublished study protocol) following PRISMA methodology. Our database search strategy could be considered to have lacked precision because it led to the retrieval of a large number of titles and abstracts. However, in this broad area of research, there is a general inconsistency in terms and definitions. For example, there is no universal definition of the term 'polypharmacy' or for the terms 'inappropriate medication', '(in)appropriate polypharmacy' [62], and 'deprescribing' [63]. A recently published systematic review confirmed the lack of consensus on the definition of 'deprescribing' [64]. Therefore, a large number of search terms was needed to cover all possible studies in this research area, and many were identified from previously published systematic reviews. Thus, we decided to accept

compromised specificity as a trade-off for optimized sensitivity in our literature search. We also conducted a search of grey literature as well as a hand search, which comprised a review of reference lists from the included studies and all identified systematic reviews on this topic (Table S8), further increasing the sensitivity of our search. Our inclusion and exclusion criteria might be interpreted as both a strength and a limitation. We targeted elderly patients (65 years or older) with polypharmacy (four or more drugs). We focused on patient-relevant outcome measures such as mortality and hospitalization, which we consider as a strength of the study. In addition, we aimed to explore the impact of strategies to reduce polypharmacy on the number of drugs being taken. As mentioned in the methods section, we not only included interventions aimed explicitly at reducing the number of drugs, but also studies aimed at optimizing drug appropriateness by identifying and eliminating inappropriate prescribing. To achieve this aim (i.e. evaluate the relationship between outcome and reduction of polypharmacy), we could only accept studies that reported the number of drugs at baseline and at follow-up. This might be seen as a limitation because we excluded studies that aimed at increasing the appropriateness of prescribing but did not report the number of drugs. However, the number of drugs was essential information to assess the effect of a reduction of polypharmacy on outcome. Our PICOS framework and literature database searches were designed to identify electronic and non-electronic interventions to reduce polypharmacy in elderly patients. However, none of the identified trials exploring the effect of an electronic intervention met our inclusion criteria. A recently updated Cochrane review on interventions to improve the appropriate use of polypharmacy for older people did not consider clinically relevant endpoints, such as mortality or change in the number of drugs as outcome measures [29]. The Cochrane review, as well as other systematic reviews, exploring the effect of improving the appropriateness of prescribing lacked an extensive analysis based on patient-relevant outcomes, and focused rather on appropriate use of polypharmacy by evaluating the effect of surrogate parameters such as PIMs or the MAI [29, 65]. Only two [41, 53] of the 12 studies included in the Cochrane review could also be included in our systematic review. All other studies did not consider a change in the number of drugs or any patient-relevant endpoint as an outcome measure, even though it has been shown that there is a linear relationship between the number of drugs and the number of ADEs and drug–drug interactions [66].

Implications for future research

When addressing polypharmacy, research groups should clearly define their methodology regarding the assessment of medication appropriateness, and they should also focus on clinically relevant outcomes such as mortality or hospital admissions whenever applicable, as these are critical in the context of polypharmacy. We should also consider involving patients and key stakeholders in the process of selecting outcomes to account for patient preferences as well as health economic and other policy or public health issues. A proper power calculation and definition of a primary endpoint (single or composite) is important to show an effect and to avoid multiple testing. Moreover, recommendations regarding the reduction of polypharmacy or the avoidance of inappropriate medication should be based on best available evidence instead of expert opinions, as done in the development of PIM lists, and by consensus or expert medication review, as performed in some of the studies we identified. There appears to be a strong need for new and better described approaches – for example, more direct and upstream interventions [67–69] (e.g. computerized physician order entry systems and evidence-based clinical decision support). In most publications, important information is lacking in the methods section. The identified strategies to reduce polypharmacy are complex interventions, and it should be stressed that study authors should provide a clear and comprehensive description of study design and intervention. We highly recommend that researchers use the Consolidated Standards of Reporting Trials statement to improve the quality of reporting of randomized controlled trials [70]. Little information is provided in the trials regarding physicians' or patients' acceptance of the intervention. Use of qualitative methodology by interviewing healthcare professionals and patients may provide useful information concerning barriers to the implementation or acceptance of an intervention.

Conclusions

This is the first systematic review exploring the effect of strategies to reduce polypharmacy to have focused explicitly on patient-relevant outcomes. The quality of current evidence to interpret the effect of strategies to reduce polypharmacy is rather weak. Interventions are complex and it is as yet unclear how ideally to assemble and implement interventions in order to achieve clinically significant improvements in multimorbid older patients with polypharmacy. There is a great need for the development of clearly defined interventions to reduce inappropriate polypharmacy, and it is essential to test these interventions in well-designed, large, long-term randomized controlled trials evaluating their effect on patient-relevant outcomes. Multimorbidity is increasing in our ageing population, and polypharmacy in older patients poses a serious threat to health and wellbeing. Even though the harms of polypharmacy are well documented in the literature, best practice models to reduce it are still lacking.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

T J prepared the study protocol, with advice from AS. TJ undertook the database searches. TJ, MA, BF, CS, EM, JH, CL, KS and AK reviewed the literature (abstracts and full texts)

and extracted data (including assessment of risk of bias) from the included studies, with arbitration by AS in the case of disagreement. The GRADE approach was assessed by TJ, MA and SK. TJ, MA, SK, EM, CS, JH, CL, AK, MF, JS and AS prepared the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.12959/suppinfo.

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